DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration
Cincinnati District Office
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July 13, 2004

WARNING LETTER
CIN-04-4746

SENT VIA FEDERAL EXPRESS

George V. Fiderio, President
Gentere, Inc. (d.b.a. Teregen Labs)
38320 Western Parkway
Willoughby, OH 44094

Dear Mr. Fiderio:

On August 19 & 21, 2003, and March 10-19, 2004, FDA inspected your firm. Concurrent inspections were performed by Compliance Specialists from the Ohio State Board of Pharmacy. As explained below, these inspections disclosed serious violations of the Federal Food, Drug, and Cosmetic Act (the Act).

As you may be aware, Section 127 of the FDA Modernization Act of 1997 amended the Federal Food, Drug, and Cosmetic Act (the Act) by adding section 503A, which specified certain conditions under which compounded human drugs could be exempt from particular requirements of the Act. In April 2002, however, the United States Supreme Court struck down the commercial speech restrictions in section 503A of the Act as unconstitutional. Accordingly, all of section 503A is now invalid. As a result, the agency has returned to its longstanding policy of exercising its enforcement discretion regarding certain types of pharmacy compounding. This policy is articulated in Compliance Policy Guide (CPG), Section 460.200 issued on June 7, 2002. The CPG contains factors that the agency considers in deciding whether to exercise its enforcement discretion. One factor is whether a firm is extemporaneously compounding reasonable quantities of drugs based on valid prescriptions from licensed practitioners for individually identified patients. Another factor is whether a firm compounds drug products that are commercially available, or which are essentially copies of commercially available FDA-approved products. In the latter case, the agency considers whether there is documentation of a particular patient's medical need for the variation from the commercially available product.

Your firm, which is not registered with FDA, produces and distributes injectable drugs without valid prescriptions for individually identified patients from licensed practitioners. Your firm makes and distributes these products in large quantities, including drugs for general sale as "office stock" to physicians and clinics. We understand that Ohio law does not permit the compounding of products for "office stock."

Many of the products that you make, including dexamethasone sodium phosphate 4mg/mL, estradiol cypionate 5mg/mL, estradiol valerate 40mg/mL, methylprednisolone acetate suspension 40mg/mL, and methylprednisolone acetate suspension 80mg/mL, are essentially copies of commercially available products. It appears that your firm cannot document a medical need for particular patients for these versions of otherwise commercially available products.

These drug products are unapproved new drugs in violation of section 505 of the Act. Because you are producing large volumes of drugs without valid prescriptions, and because many of these drugs are essentially copies of commercially available products, we will not exercise our enforcement discretion with regard to this violation.

In addition, these drug products are misbranded under section 502(f)(1) of the Act because their labeling fails to bear adequate directions for use and they are not exempt from this requirement under 21 CFR § 201.115.

The products are also misbranded under section 502(o) of the Act in that they are manufactured in an establishment not duly registered under section 510 of the Act, and the articles have not been listed as required by section 510(j) of the Act. Your facility is not exempt from registration and drug listing requirements under 21 CFR § 207.10 or section 510(g) of the Act. For the reasons stated above, we will not exercise enforcement discretion regarding these violations.

Your drug products are also adulterated under section 501(a)(2)(B) of the Act because the controls and procedures used in their manufacture, processing, packing, and holding do not conform to current good manufacturing practices regulations, 21 CFR Parts 210 and 211. Deviations from these regulations include, but are not limited to, the following:

1. The flow of drug product containers, closures, and drug products though the building is not designed to prevent contamination (21 CFR 211.42(b)).

   Specifically: Sterilized glassware (including mixing beakers and product vials), containers of sterilized product, and bags of sterilized stoppers are carried through the unclassified workroom and the class 10,000 compounding room in order to get them into the filling room. The hot air ovens and autoclaves do not open into the filling room.

2. Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not followed and do not include validation of the sterilization process (21 CFR 211.113(b)).

   Specifically:

   a. The oven used to sterilize filled vials of the oil products and the autoclaves used to sterilize bulk beakers of suspension products have not been validated for these purposes.

   b. The beakers of sterilized suspensions only had a "muff" over the top. The sterilized glassware and vials only had a single cover of aluminum foil over them. One tray of vials that was used had a patch over a hole in the aluminum foil. Studies have not been performed to assure the aluminum foil and muffs adequately protect the sterilized items during their transfer from the sterilizers through the unclassified work area and class 10,000 room and their storage in the class 1000 room until use.

   c. Media fills have not been performed to assure the aseptic procedures were adequate.

   d. Smoke studies have not been performed to demonstrate acceptable air flow in and around the filling hoods.

   e. Validation of the autoclave used to sterilize bags of stoppers did not involve placing

biological indicators inside bags of stoppers.

f. Settling plates are set flat on the work surface in the horizontal flow filling hoods.

g. There is no validation study for the filters used to sterilize batches of solutions to assure product compatibility and effectiveness.

h. The integrity of the sterilizing filters was assessed before and after filtration by checking the bubble point. No minimum specification had been set. Most post-filtration bubble points were below the filter manufacturer's integrity specification of 50 psig. Bubble points as low as 30 psig were accepted even though no studies had been performed to show these levels would be acceptable.

i. Operators who set up the filling equipment and filled and stoppered vials by hand touched many items other than the sterilized vials and stoppers. Many of these items were outside the filling hood. They resumed the filling operation without putting on a new pair of sterile gloves. Many times they did not even sanitize their gloves with the alcohol that was available. These items included paper, pen, plug and electrical cord that were on the floor, stopper bags, aluminum foil, equipment cart, chair, vial trays, trash can, hood table, and pump control pad.

j. Some of the stoppers that fell onto the work surface of the filling hood were put onto filled vials or put back into the stopper bowl.

k. Sterilized suspensions are homogenized in the filling hood. The homogenizer is assembled in the hood. A plastic cover that had been sanitized but not sterilized was pushed over the product contact end of the homogenizer.

l. The batch record for one product has instructions to loosen the drug that adhered to the bottom of the beaker after sterilization using a hand held sterilized spatula.

m. Exposed stoppers and sterilizing filters were transferred between the two Class 100 hoods.

n. Unwrapped stoppers that remained in the filling hood overnight were used to stopper product the next day.

o. The aluminum foil that was removed from the trays of vials was put back over unused vials that would be used for a later filling operation.

p. Sanitized but not sterilized equipment was placed into and used in the filling hood. This included the keypad for the filling pump and the stand and motor for the homogenizer.

q. There was no study to show the cushioned chair in the filling room did not expel viable and/or non-viable particulates when the operator sat on it.

r. Color changing tape or other visual indicators are not used to differentiate items that have gone through a sterilization cycle from those that have not.

s. One filling operator pulled her second glove into place by grasping the folded cuff with the other gloved hand (rather than sliding the other gloved hand between the cuff and the sterile outer surface as instructed in SOP 008). Another operator pushed her sleeves under the gloves with the other sterile gloved hand.

3. Batch production and control records do not include complete information relating to the production and control of each batch (21 CFR 211.188).

Specifically: There was no temperature chart or recording of the time and temperature during the sterilization of several lots of oil products. For some lots that had a manual recording of the temperature, the record did not document that the minimum temperature was maintained for the required two hours.

4. Control systems used to prevent contamination during aseptic processing operations do not include floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable (21 CFR 211.42(c)(10)(i)).

Specifically: The filling room has a textured linoleum floor with no coving where the floor meets the walls.

5. Control systems for monitoring environmental conditions during aseptic processing operations are inadequate (21 CFR 211.42(c)(10)(iv).

Specifically: Environmental monitoring for filling operations does not include the operator's gown and gloves.

6. Protective apparel is not worn as necessary to protect drug products from contamination (21 CFR 211.28(a)).

Specifically: Goggles did not enclose the skin around the eyes of a filling operator.

7. Unexplained discrepancies in batch production records are not thoroughly investigated. There is no documentation of follow-up (21 CFR 211.192).

Specifically: Investigations were not conducted when environmental samples exceeded the action levels as required by SOP 520.

8. There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

Specifically:

a. There is no process validation to assure homogeneity for the manufacture of products except for Dexamethasone 8 mg.

b. Process validation for Dexamethasone 8 mg involved testing only five samples per lot for potency (one from each of the two beakers and three vials). There was no statistical analysis of the assay results.

c. Written procedures in the batch records:
(1) lack mixing speeds and times
(2) lack instructions to mix after the final QS step
(3) lack instructions to mix the two beakers for a lot of Pyridoxine together prior to filling
(4) lack temperature settings
(5) include hand mixing steps
(6) do not specify what size of stir bar to use
(7) do not address the issue of foaming or the allowable amount of foam during filling

9. The master production and control records for each batch size of drug product are not prepared, dated, and signed by one person with a full handwritten signature and independently checked, dated, and signed by a second person (21 CFR 211.186(a)).

10. Batch production and control records do not include the identification of the persons performing and checking each significant step in the operation (addition of ingredients and completion of manufacturing steps), for each batch of drug product produced (21 CFR 211.188(b)(11)).

11. Written production and process control procedures are not followed in the execution of production and process control functions (21 CFR 211.100(b)).

Specifically: The batch record for lot 041103A indicated that mixing should continue until a clear solution was formed prior to putting the beaker on the scale for the addition of the polysorbate 80. Crystals were observed in the bottom of the beaker when it was transferred to the scale for the addition of the polysorbate 80.

12. All compounding and storage containers used during the production of a batch of drug product are not properly identified at all times to indicate the phase of processing of the batch (21 CFR 211.105(a)).

Specifically: During the filtering of lot 041003A, a beaker containing filtered product was next to an identical beaker of unfiltered product with no visible distinction between the two beakers.

13. Equipment and utensils are not cleaned at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product (21 CFR 211.67(a)).

Specifically: Cleaning validation involved testing for residues of the cleaning compound but not for residues of the various products for which the beakers, stir bars, and homogenizer had been used.

14. Laboratory controls do not include the establishment of scientifically sound and appropriate specifications designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity (21 CFR 211.160(b)).

Specifically:

a. Most of the USP labeled products are not tested to assure they meet all of the USP specifications. They are tested only for potency, sterility, endotoxins, and pH.

b. Products are filled into multi-dose vials that contain preservatives. There are no specifications for or assays performed to determine the levels of these preservatives in the finished products.

c. There are no endotoxin specifications for most of the products.

15. Written procedures for sampling and testing plans are not followed for each drug product (21 CFR 211.165(c)).

Specifically: The number of vials to be tested for sterility was to follow the requirements in the USP. There were instances where fewer vials were sent to the testing laboratory than were indicated in the USP.

16. An adequate number of batches of each drug product are not tested to determine an appropriate expiration date (21 CFR 211.166(b)).

Specifically: For most products, there was no stability data to support the 6 month expiration dates. For the remaining products, the stability data used to support the six month expiration dates were inadequate. Six products had data for only one lot. For two of these products, the assays were below specifications.

17. The accuracy and reproducibility of test methods have not been established (21 CFR 211.165(e)).

Specifically: Visual examinations for particulates in the filled amber vials were performed in front of a bright light without the aid of white and black backgrounds. Although many vials were rejected due to particulates, this inspection system has not been validated to assure that all vials with particulates were identified.

18. Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without performing at least one specific identity test on each component and establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals (21 CFR 211.84(d)(2)).

Specifically:

a. For most products, the raw materials, including the active ingredients, are accepted based solely on the receipt of a Certificate of Analysis (COA) from the supplier. The reliability of the supplier's COAs is not periodically verified.

b. For most raw materials, identity tests are not performed.

19. A sample which is representative of each lot in each shipment of each active ingredient is not retained (21 CFR 211.170(a)).

Specifically: Reserve samples of many active ingredients were not maintained.

20. Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel (21 CFR 211.68(b)).

Specifically: Batch records are printed from the computer as they are needed. There are no controls to limit access to the files containing the batch records.

The above violations are not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure that all drug products compounded and processed by your firm are in compliance with federal laws and regulations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in additional regulatory action without further notice. These actions include, but are not limited to, seizure of your products or injunction. Federal agencies are routinely advised of warning letters issued so that they may take this information into account when considering the award of government contracts.

Please notify this office in writing within 15 working days of receipt of this letter of the additional specific steps you will take to correct these violations, including an explanation of each step being taken to prevent the recurrence of the violations. You should address your reply to this letter to Charles S. Price, Compliance Officer, U. S. Food and Drug Administration, 6751 Steger Drive, Cincinnati, OH 45237.

Sincerely,

Carol A. Heppe
District Director
Cincinnati District